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Letter to the Editor

Letter in response to the article: Vitamin D concentrations and COVID-19 infection in UK biobank (Hastie et al.)

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To the Editor:

The recent article by Clair Hastie and colleagues reported that while 25-hydroxyvitamin D [25(OH)D] concentration below 25 nmol/l was a significant risk factor for confirmed COVID-19 infection [odds ratio (OR) = 1.37 (95% confidence interval (CI), 1.07 to 1.76)] it was not in a multivariable model [OR = 0.92 (95% CI 0.71 to 1.21)] [1]. The multivariable model was adjusted for ethnicity, sex, month of assessment, Townsend deprivation quintile, household income, self-reported health rating, smoking status, BMI category, age at assessment, diabetes, SBP, DBP, and long-standing illness, disability or infirmity.

The statistical error is that the multivariable model was over adjusted due to including factors that are likely mediators of disease rather than confounding factors. Statistical criteria and causal diagrams should be utilized to identify confounders and communicate assumptions being made [2,3]. Multiple causal structures between 25(OH)D and COVID-19 infection may be equally plausible so we suggest performing multiple analyses with both simple and complex models.

Additionally, we suggest stratifying the analysis by ethnicity to help clarify the relationship between ethnicity, 25(OH)D and COVID-19 infection. For example, an observational study was conducted in South Carolina, USA with pregnant women of various ethnic groups: white, 488; African American, 395; Hispanic, 117; Asian/Pacific Islands, 19; multiple or other, 39 [4]. Women were given free vitamin D3 and counseled to supplement to achieve >100 nmol/l. Comparing those who achieved ≥ 100 nmol/l to those <50 nmol/l, a similar decreased risk was observed for white women (OR = 0.35, 95% CI = 0.13–0.92) and non-white women (OR = 0.32, 95% CI = 0.14–0.74) indicating that 25(OH)D was a significant risk factor for both ethnic categories.

Further, it should be stated as a limitation that the outcome measure, the presence or absence of positive COVID-19 test results from Public Health England, is currently a limited proxy for COVID-19 infection. Also, it is possible that this participant population did not have high enough 25(OH)D concentrations to observe a measurable effect after adjustment for other factors; concentrations

closer to 100 nmol/l may be needed.

Declaration of competing interest

WBG receives funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR USA). Grassroots Health works with various supplement suppliers to test the efficacy of their products in various custom projects. These suppliers may be listed as 'Sponsors' of Grassroots Health.

Response to letter of grant and McDonnell regarding the article: Vitamin D concentrations and COVID-19 infection in UK biobank (Hastie et al.)

We thank Drs Grant and McDonnell for their interest in our paper. However, we respectfully disagree with their arguments. To be a mediator, 25(OH)D concentration would need to be causally related to the variable. It is not plausible that 25(OH)D concentration causes age, sex, ethnic group, deprivation, adiposity, smoking status, deprivation, or the month of assessment. In terms of baseline health, whilst vitamin D deficiency is linked to some specific health outcomes, impaired health more widely is also associated with reduced physical activity and therefore time spent outdoors. We have run an intermediate model containing age, sex, ethnicity, area deprivation, income, obesity, smoking and month of assessment as covariates, but not including any of the health-related covariates and the associations remained non-significant, thereby refuting the suggestion that the lack of significance could be attributed to over-adjustment or inclusion of potential mediators.

Vitamin D continuous OR = 1.00; 95% CI 0.997–1.01; $p = 0.426$

Vitamin D deficient OR = 0.97; 95% CI 0.74–1.28; $p = 0.852$

Vitamin D insufficient OR = 0.92; 95% CI 0.75–1.13; $p = 0.409$

There was no statistical interaction between vitamin D deficiency and ethnicity. Since ethnicity was not an effect modifier, there will be no significant difference in the association between 25(OH)D concentration and covid-19 by ethnic group.

A positive Covid-19 test result from Public Health England confirms infection. We have already acknowledged in the paper that some people with asymptomatic or mild disease will not have been tested. Therefore, it is likely to ascertain more severe infections.

25(OH)D concentration <100 nmol/l is not an accepted definition of vitamin D deficiency. Indeed, in the UK population, which is predominantly white, the mean 25(OH)D concentration is 43.5 nmol/l for men aged 19–64 years, and 47.3 nmol/l for women aged 19–64 years [1].

Reference

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